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Saffron (adjunct) for people with schizophrenia who have antipsychotic-induced metabolic syndrome (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Saffron (adjunct) for people with schizophrenia who have antipsychotic-induced metabolic syndrome

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To investigate the effects of saffron as an adjunct treatment for people with schizophrenia who have antipsychotic-induced metabolic syndrome.

BACKGROUND

Description of the condition

Schizophrenia is a serious and chronic mental illness that affects how a person feels, thinks and behaves. Symptoms of schizophrenia usually start in early adulthood, between the age of 16 and 30 years (National Institute of Mental Health 2016). Men tend to develop schizophrenia at earlier ages than women. The prevalence of schizophrenia has been estimated as 1.1% of the population over the age of 18 years (National Institute of Mental Health 2016). Schizophrenia has three major categories of symptoms. Positive or psychotic symptoms, where a person's experiences hallucinations, delusions and thought disorders; negative symptoms such as a difficulty with showing normal emotional response and behaviours (including "flat affect" , reduced feelings of pleasure, and reduced speaking); and cognitive symptoms that affect a person's memory or other aspects of thinking. These symptoms include problems with using information, decision making and paying attention (National Institute of Mental Health 2016).

Description of the intervention

Antipsychotic medication is the mainstay treatment for people with schizophrenia (Galletly 2016). However, antipsychotics can have debilitating side effects (Leucht 2013; Galletly 2016; Solmi 2017). Development of newer antipsychotic drugs has provided great advantages to people with schizophrenia (Galletly 2016). With their fewer extrapyramidal side effects (EPS) than older antipsychotics, and their greater efficacy in reducing the neg-

ative symptoms (González-Pardo 2007; Popović 2015). However, a large body of evidence suggests that long-term treatment with some newer antipsychotics (such as olanzapine) is associated with an increased risk of metabolic side effects including hyperglycaemia (high blood glucose (sugar) levels, hyperlipidaemia (raised lipid (fat) levels, type 2 diabetes mellitus and weight gain (Lieberman 2004; González-Pardo 2007; Leucht 2009; Bartoli 2013). These symptoms are currently referred to as metabolic syndrome, which place patients at significant risk of stroke, coronary heart disease and other serious disorders (Bartoli 2015; Sahlberg 2015). Often adjunct treatments can be given with both newer and first-generation antipsychotics to help counteract their adverse effects (Chen 2015; Solmi 2017)

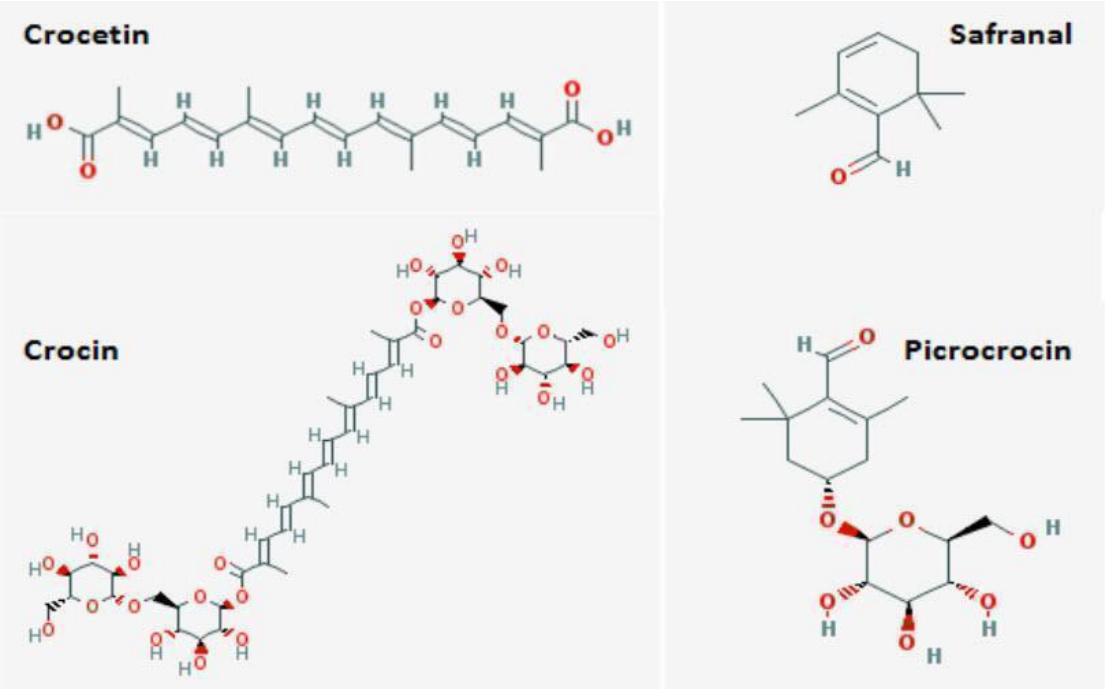
Crocus sativus (saffron) is a spice derived from 'saffron crocus' and was cultivated originally in Iran, Spain, Greece and India (Figure 1; Figure 2). It is widely used as a food additive across the world. However, it has been used as a medicinal plant in traditional Iranian medicine for treatment of a wide range of disorders including depression, seizures, cognitive disorders, cancers, asthma, liver diseases, menstruation disorders and pain (Kianbakht 2011; Kianbakht 2015).

Figure 1. Saffron flower

Figure 2. Dried saffron stigmata

Saffron has three major active constituents including crocin (crocetin glycoside), crocetin, and safranal (Kianbakht 2011) (Figure 3). Saffron and its active constituents have demonstrated a wide range of pharmacological properties in previous experimental studies including, anti-inflammatory, anti-oxidative (Srivastava 2010, Kamalipour 2011, Mashmoul 2013), anti-hyperlipidaemic, anti-diabetic and insulin resistance (Mashmoul 2013). Table 1 summarises the principal pharmacological properties of saffron constituents.

Figure 3. Chemical composition of the most active constituents of saffron (Mashmoul 2013)



With the potential hypoglycaemic and anti-diabetic effects, saffron and its active constituents have also been found to prevent metabolic syndrome and insulin resistance in schizophrenia (Fadai 2014).

How the intervention might work

Saffron and its active constituents have demonstrated a variety of pharmacological effects against obesity and related metabolic disorders that are classified in three major categories including:

Hypolipidaemic effect of saffron

Crocin, one of the major bioactive constituents of saffron, has been reported as an effective hypolipidaemic agent in a group of experimental studies (He 2005; Sheng 2006; Zhiyu 2009; Shirali 2013). Crocin demonstrated strong triglyceridaemic and cholesterolaemic lowering effects in rats and quails (He 2005; Sheng 2006). Further studies confirmed that crocin could reduce the amount of cholesterol and malondialdehyde once maintaining the level of serum nitric oxide in hyperlipidaemic animals (He 2007). The hypolipidaemic mechanism of crocin could be explained by the effective inhibition of cholesterol and dietary fat absorption through blocking the activity of enzymes related to fat metabolism including pancreatic lipase (Mashmoul 2013; Hassan 2015). An earlier study suggested that crocin has higher selectivity for pancreatic lipase (Mashmoul 2014).

Hypoglycaemic and anti-diabetic effects of saffron

The role of saffron and its bioactive constituents in significantly enhancing insulin sensitivity and reducing blood glucose in diabetic rats has been highlighted before (Mashmoul 2013). Both crocin and safranal were found to demonstrate anti-diabetic and antihyperglycaemic effects in rats. The saffron extracts, crocin and safranal, significantly reduced HbA1C and blood glucose levels as well as improving insulin levels in the alloxan-induced diabetic rats without hepatic and renal toxicities (Kianbakht 2011).

The mechanism by which, saffron and its bioactive constituents reduced blood glucose and improved insulin levels has been investigated. In one study, saffron was suggested to strongly improve glucose uptake and phosphorylation of AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) and mitogen-activated protein kinases(MAPKs), but not phosphatidylinositol 3-kinase (PI 3-kinase)/Akt (Kang 2012). The hypoglycaemic effect of safranal has been well investigated (Mashmoul 2013; Samarghandian 2013). Maeda 2014 demonstrated mechanisms by which safranal reduces blood glucose in rats as a principal PTP1B inhibitor and by inducing a ligand-independent activation of insulin signalling in cultured myotubes. It has been also suggested that safranal has significantly increased glucose uptake through the translocation of glucose transporter in rats (Maeda 2014).

Satiety enhancer and weight loss promoter

Decreased appetite has been repeatedly suggested as a clinical com-

plication and adverse effects of saffron consumption. This could be primarily explained by the anti-depressant and mood-improving effects of saffron that could reduce appetite and snacking in humans (Gout 2010; Mashmoul 2013). Saffron could potentially effect weight loss processes through four major mechanisms including: decreasing calorie intake by inhibition of pancreatic lipase, acting as an antioxidant agent, reducing food intake by enhancing satiety and improving lipid and glucose metabolism (Mashmoul 2013).

Why it is important to do this review

People with schizophrenia are often not prescribed or stop taking newer antipsychotics because of the serious risk of metabolic side effects which can put them at a higher risk of developing additional health problems (Chen 2015). In this context, treatment of people with schizophrenia is associated with the right balance of safety versus effectiveness. While evidence on the use of newer antipsychotic drugs and their benefits are available, an ongoing debate about patient safety questions the wide use of these drugs for schizophrenia (Lieberman 2004; González-Pardo 2007; Bartoli 2015), and more research into identifying efficient and safe treatment for schizophrenia is required.

Medicinal plants are among the adjunct alternatives that could reduce the clinical complications and adverse effects of current treatments especially for people with schizophrenia. Saffron, a well known spice, has several potential therapeutic properties including antioxidant, antihyperglycaemic and anti-obesity effects. In addition, saffron has demonstrated tolerability and few adverse effects in human and animal studies (Kianbakht 2011; Mashmoul 2013; Fadai 2014; Kianbakht 2015). With these pharmacological properties, saffron and its bioactive constituents could be considered as an adjunct treatment for reducing metabolic syndrome symptoms. There is currently no evidence on the clinical efficacy of saffron for people with schizophrenia, and this review will evaluate the evidence available for using herbal supplements in managing prevalent adverse effects of current treatments for schizophrenia.

OBJECTIVES

To investigate the effects of saffron as an adjunct treatment for people with schizophrenia who have antipsychotic-induced metabolic syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. If a trial is described as 'double-blind' but implies randomisation, we will include such trials in a sensitivity analysis (see Sensitivity analysis). We will exclude quasi-randomised studies, such as those allocating by alternate days of the week. Where people are given additional treatments within saffron, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the saffron that is randomised.

Types of participants

Adults aged over 18 years with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, already on antipsychotic treatment and have also reported metabolic-related symptoms

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible so propose to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent), and as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Saffron aqueous extract or its bioactive constituents

Any dose or mode of administration, in addition to standard care

2. Placebo or no treatment

Any dose or mode of administration

3. Any other treatment

Any dose or mode of administration

Types of outcome measures

We aim to divide all outcomes into short term (less than six months), medium term (seven to 12 months) and long term (over one year).

Primary outcomes

1. Metabolic syndrome

1.1 Clinically important improvement in metabolic syndrome-related symptoms - as diagnosed and defined by each of the studies - for example, weight gain

1.2 Improvement in insulin resistance in patients already on antipsychotics

Secondary outcomes

1. Global state

1.1 Clinically important change in global state

1.2 Relapse - as defined by each study

1.3 Any change in global state

1.4 Average endpoint or change score global state scale

1.5 Use of other medications

2. Mental state

2.1 General

2.1.1 Any change in general mental state - as defined by each of the studies

2.1.2 Average endpoint or change score general mental state scale

2.2 Specific

2.2.1 Clinically important change in specific symptoms - as defined by each of the studies (positive, negative, affective, cognitive symptoms of schizophrenia)

2.2.2. Any change in specific symptoms - as defined by each of the studies (positive, negative, affective, cognitive symptoms of schizophrenia)

2.2.3 Average endpoint or change score specific symptom scale

3. Adverse effects (of the adjunct treatment with saffron)

3.1 General adverse effects

3.1.1 At least one adverse effect

3.1.2 Clinically important adverse effects - as defined by each of the studies

3.1.3 Average endpoint/change scores adverse-effect scales

3.2 Specific adverse effects - clinically important - as defined by each of the studies

3.2.1 Anticholinergic

3.2.2 Cardiovascular

3.2.3 Central nervous system

3.2.4 Gastrointestinal

3.2.5 Endocrine (e.g. amenorrhoea, galactorrhoea, hyperlipidaemia, hyperglycaemia, hyperinsulinaemia)

3.2.6 Haematology (e.g. haemogram, leukopenia, agranulocytosis/neutropenia)

3.2.7 Hepatitic (e.g. abnormal transaminase, abnormal liver function)

3.2.8 Metabolic

3.2.9 Movement disorders

3.2.10 Various other

3.2.11 Average endpoint or change score on specific adverse effect scale

4. Quality of life (recipient or informal carers or professional carers)

4.1 Overall

4.1.1 Clinically important change in quality of life - as defined by each of the studies

4.1.2 Any change in quality of life - as defined by each of the studies

4.1.3 Average endpoint or change score on quality of life scale

4.2 Specific

4.2.1 Clinically important change in specific aspects of quality of life - as defined by each of the studies

4.2.2 Any change in specific aspects of quality of life - as defined by each of the studies

4.2.3 Average endpoint or change score on specific aspects of quality of life scale

5. General functioning

5.1 Overall

5.1.1 Clinically important change in general functioning - as defined by each of the studies, including working ability

5.1.2 Any change in general functioning - as defined by each of the studies, including working ability

5.1.3 Average endpoint or change score on general functioning scale

5.2 Specific

5.2.1 Clinically important change in specific aspects of functioning, such as life skills- as defined by each of the studies

5.2.2 Any change in specific aspects of functioning, such as life skills- as defined by each of the studies

5.2.3 Average endpoint or change score on specific aspects of functioning scale, such as life skills- as defined by each of the studies

5.2.4 Any change in educational status, as defined by each study

5.2.5 Any change in employment status, as defined by each study.

6. Social functioning

6.1 Clinically important change in social functioning - as defined by each of the studies

6.2 Any change in social functioning - as defined by each of the studies

6.3 Average endpoint or change score on social functioning scale

6.4 Substantial improvement/no improvement in target function - as defined by each of the studies e.g. social skills.

7. Death

7.1 Any cause except suicide and homicide

7.2 Suicide

7.3 Homicide

8. Satisfaction with care (recipients of care or carers) (including subjective well-being and family burden)

8.1 Recipient

8.1.1 Clinically important change in satisfaction - as defined by each of the studies
8.1.2 Recipient of care satisfied/not satisfied with treatment
8.1.3 Recipient of care average endpoint or change score on satisfaction scale
8.2 Carers (including health professionals)
8.2.1 Clinically important change in satisfaction - as defined by each of the studies
8.2.2 Carer satisfied/not satisfied with treatment (General impression of carer/other)
8.2.3 Carer average endpoint or change score on satisfaction scale
9. Leaving the study early

9.1 For any reason
9.2 Due to inefficacy
9.3 Due to adverse effect

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schünemann 2011) and will use GRADEpro GDT to export data from our review to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as important to patient-care and decision making. We aim to select the following main outcomes for inclusion in the 'Summary of findings' table.

1. Metabolic syndrome: clinically important improvement in metabolic syndrome related symptoms - e.g. weight gain
2. Metabolic syndrome : improvement in insulin resistance
3. Global state: clinically important change in global state - as defined by each of the studies,
4. Quality of life: clinically important change in quality of life - as defined by each of the studies
5. General functioning: clinically important change in general functioning, including working ability- as defined by each of the studies
6. Satisfaction with care: clinically important change in satisfaction with care - as defined by each of the studies
7. Leaving the study early: due to adverse effects

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The Information Specialist will search the register using the following search strategy:
saffron in Intervention Field of STUDY
In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics.
This register is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group' s Module). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the included or awaiting assessment studies tables.

Data collection and analysis

Selection of studies

Review author MZ will independently inspect citations from the searches and identify relevant abstracts. Review author SMM will independently re-inspect a random 20% sample of these abstracts to ensure reliability. Where disputes arise, we will acquire the full report for more detailed scrutiny. AB will then obtain and inspect full reports of the abstracts or reports meeting the review criteria. RMA, again, will re-inspect a random 20% of these full reports in order to ensure reliable selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors MZ and AB will extract data from all included studies. In addition, to ensure reliability, SMM will independently

extract data from a random sample of these studies, comprising 10% of the total. We will attempt to extract data presented only in graphs and figures whenever possible, but include only if two review authors independently have the same result. . If studies are multi-centre, where possible, we will extract data relevant to each. We will discuss any disagreement and document decisions. If necessary, we will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. With remaining problems review author RMA will help clarify issues and we will document these final decisions.

2. Management

2.1 Forms

We will extract data onto standard, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000);
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
c) the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable. However there are exceptions, we will include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' we will note if this is the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if the former are not available. If necessary, we will combine endpoint and change data in the analysis as we prefer to use mean differences (MD) rather than standardised mean differences(SMD) throughout (Higgins 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we will apply the following standards to relevant continuous data before inclusion.
For endpoint data from studies including fewer than 200 participants:
a) when a scale starts from the finite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher than one but less than two, there is suggestion that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially. If such data change results we will enter as 'other data'. Finally, if the ratio is larger than two we will include these data, because it is less likely that they are skewed (Altman 1996; Higgins 2011).
b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we will modify the calculation described above to take the scale starting point into account. In these cases skewed data are present if 2 SD > (S − S min), where S is the mean score and 'S min' is the minimum score.
Please note: we will enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether or not data are skewed.

2.5 Common measure

To facilitate comparison between trials we intend, if necessary, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will make efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005;, Leucht 2005a). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for saffron aqueous extract or its active constituents. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved'), we will report data where the left of the line indicates an unfavourable outcome and note this in the relevant graphs.

Assessment of risk of bias in included studies

Again, review authors AB and MZ will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a) to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, we will make the final rating by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise as to which category a trial is to be allocated, again, we will resolve by discussion.

We will note the level of risk of bias in both the text of the review, a 'Risk of bias summary and a 'Risk of bias' graph, and a 'Summary of findings' table.

Measures of treatment effect

1. Binary data

For binary outcomes, we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval. It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The number needed to treat for an additional beneficial outcome (NNTB)/ number needed to treat for an additional harmful outcome (NNTH) statistic with its confidence intervals is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, where possible, we will calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes, we will estimate mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate effect size and transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we will only use data of the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary, we will simply add these and combine within the two-by-two table. If data are continuous, we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more than 50% of data be unaccounted for, we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table/s by down-rating quality. Finally, we will also downgrade quality within the 'Summary of findings' table/s should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes, the rate of those who stay in the study - in that particular arm of the trial - will be used for those who did not. We will undertake a sensitivity analysis to test how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We will reproduce and use data where attrition for a continuous outcome is between 0% and 50%, and data only from people who complete the study to that point are reported.

3.2 Standard deviations

If standard deviations (SDs) are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either 'P' value or 't' value available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011): When only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. If these formulae do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers, others use the method of last observation carried forward (LOCF), while more recently, methods such as multiple imputation or mixed effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, we will preferably use the more sophisticated approaches, e.g. we will prefer to use MMRM or multiple-imputation to LOCF and we will only present completer analyses if some kind of ITT data are not available at all. Moreover, we will address this issue in the item "incomplete outcome data" of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for clearly outlying people or situations which we had not predicted would arise and discuss such situations or participant groups,

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise and discuss any such methodological outliers.

3. Statistical heterogeneity

3.1 Visual inspection

We will visually inspect graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). We will interpret an I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, as evidence of substantial levels of heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions)* (Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies are of similar sizes. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

No subgroup analysis anticipated.

1.2 Clinical state, stage or problem

We propose to undertake this review and provide an overview of the effects of saffron aqueous extract or its active constituents for people with schizophrenia in general. In addition, however, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

We will report if inconsistency is high. First, we will investigate whether data have been entered correctly. Second, if data are correct, we will visually inspect the graph and we will successively remove outlying studies to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we will present data. If not, we will not pool these data but will discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.
When unanticipated clinical or methodological heterogeneity are obvious, we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

If there are substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we will not add data from the lower-quality studies to the results of the higher-quality trials, but will present these data within a subcategory. If their inclusion does not result in a substantive difference, they will remain in the analyses.

1. Implication of randomisation

If trials are described in some way as to imply randomisation, for the primary outcomes, we will pool data from the implied trials with trials that are randomised. If their inclusion does result in clinical, but not necessarily statistically significant differences, we will not add the data from these lower-quality studies to the results of the higher-quality trials, but will present these data within a subcategory.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see Dealing with missing data), we will compare the findings of the primary outcomes when we use our assumption compared with completer data only. If there is a substantial difference, we will report results and discuss them, but continue to employ our assumption.

Where assumptions have to be made regarding missing SDs (see Dealing with missing data), we will compare the findings on primary outcomes when we use our assumption compared with completer data only. We will undertake a sensitivity analysis to test how prone results are to change when 'completer' data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are at high risk of bias across one or more of the domains (see Assessment of risk of bias in included studies) for the meta-analysis of the primary outcome.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we use imputed values for ICC in calculating the design effect in cluster-randomised trials.

5. Fixed- and random-effects

We will synthesise data using a random-effects model however, we will also synthesise data for the primary outcome using a fixed-effect model to evaluate whether this alters the significance of the results.

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The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required. We would like to thank Sri Mahavir Agarwal and Nyuk Jet Chong for peer reviewing this protocol.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Table 1: principal pharmacological properties of *Crocus sativus*

Health Property	Saffron Compound	Human/animal participants	Results	Reference
Hypolipidaemic	Crocin Crocetin Crocin Saffron and crocin	Bovine aortic endothelial cells (EC), bovine aortic smooth muscle cells (SMC) and quail Quails Rats Albino Wistar rats	Crocin decreased OX-LDL induced EC apoptosis as well as SMC proliferation Crocin decreased Ox-LDL and thus inhibited the formation of atherosclerosis in quails A 9-week treatment with crocetin (25 mg, 50 mg, 100 mg/kg/day) reduced serum total cholesterol level and inhibited the formation of aortic plaque, reduced malondialdehyde and decreased nitric ox-	He 2005 He 2007 Sheng 2006 Asdaq 2010

Table 1. Table 1: principal pharmacological properties of *Crocus sativus* (*Continued*)

			ide in serum A 10-day treatment with crocin (25 mg to 100 mg/kg/day) significantly reduced serum triglyceride, total cholesterol, LDL cholesterol and VLDL cholesterol levels The hyperlipidaemic effect of crocin was attributed to its pancreatic lipase inhibition Oral administration of saffron (25 mg, 50 mg, and 100 mg/kg) or crocin (4.84 mg, 9. 69 mg, and 19.38 mg/kg) for 5 days indicated significant reduction in serum levels of triglyceride, total cholesterol, alkaline phosphatase	
Hypoglycaemic & Anti-diabetic	Crocetin Saffron methanolic extract, crocin and safranal Saffron Extract Crocetin Crocin	Male Wistar rats Alloxan-diabetic Rats Healthy male rats Male Wistar rats Neonatal male Wistar rats	Crocetin (40 mg/kg) prevented dexamethasone-induced insulin resistance Saffron methanolic extract (80 mg and 240 mg/kg), crocin (50 mg and 150 mg/kg) and safranal (0.25 mLand 0.5 mL/kg) significantly reduced the fasting blood glucose and HbA1c levels and significantly increased the blood insulin levels without any significant effects on the blood SGOT, SGPT and creatinine levels in the diabetic rats compared with compared with the control diabetic rats Administration of 50 mg/kg of saffron extract	Xi 2005 Plants 2011 Arasteh 2010 Xi 2007 Shirali 2012

Table 1. Table 1: principal pharmacological properties of *Crocus sativus* (*Continued*)

			for 14 days significantly decreased serum glucose, cholesterol and insulin levels Crocetin (40 mg/kg) improved insulin sensitivity in fructose-fed rats via normalizing the expression of both protein and mRNA of adiponectin (an insulin-sensitizing adipocytokine), TNF-α, and leptin in epididymal white adipose tissue Administration of crocin (50 mg or 100 mg/kg) significantly reduced serum glucose and advanced glycation end products. It also caused substantial lower levels of triglyceride, total cholesterol, and LDL in rates receiving crocin for 2 months	
Satiety enhancer and weight loss promoter	Capsulated ethanolic saffron extract Saffron methanolic extract, crocin	Sixty overweight Women Adult male Wistar rat	Participants were given 1 capsule of Satiereal (176.5 mg/day) or an inactive placebo with no limitation in dietary intake. After 2 months, the participants using the saffron extract reported a decrease in snacking and lost more weight than the control group Participants were given saffron methanolic extract (25 mg, 50 mg, 100, 200 mg/kg) and crocin (5 mg, 15 m, 30 mg, 50 mg/kg), sibutramine (5 mg/kg) and saline for 2 months. Findings indicated significant reductions of body weight, food intake and leptin levels in	Gout 2010 Kianbakht 2015

Table 1. Table 1: principal pharmacological properties of *Crocus sativus* (*Continued*)

			rats receiving saffron and crocin compared with saline and baseline	

LDL: low-density lipoprotein
SGOT: Serum glutamic oxaloacetic transaminase
SGPT: Serum glutamic pyruvic transaminase
This table was partly obtained from Mashmoul 2013.

CONTRIBUTIONS OF AUTHORS

Azam Bazrafshan developed the protocol.

Morteza Zare developed the protocol.

Reza Malekpour Afshar developed the protocol.

Seyed Mohammad Mazloomi developed the protocol.

DECLARATIONS OF INTEREST

Morteza Zare: none known.

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External sources

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